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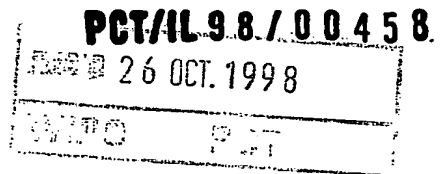
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121793	Number
17-09-1997	תאריך: Date
	הוקדם/נדחה Ante/Post-dates

בקשה לפטנט

Application for Patent

C:28519

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(בעברית)
(Hebrew)

ISOTOPIC GAS ANALYZER

(באנגלית)
(English)

hereby apply for a patent to be granted to me in respect thereof

מבקש בזאת כי ינתן לי עליה פטנט

<p>* בקשה חלוקה - Application for Division</p>		<p>* דרישה דין קדימה Priority Claim</p>		
<p>* לבקשה/לפטנט to Patent/Appl.</p>		מספר/סימן Number/Mark	תאריך Date	מדינת האיגוד Convention Country
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מנתח גזים איזוטופיים

ISOTOPIC GAS ANALYZER

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Ilan Ben Oren
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C:28519

ספגס תעשיות בע"מ
הממציאים: אפרים קרליבך
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ISOTOPIC GAS ANALYZER

FIELD OF THE INVENTION

This invention relates to the field of analyzers for determining the isotopic ratio of gases, especially in exhaled breath.

BACKGROUND OF THE INVENTION

Infra-red gas absorption can be used as a means of analyzing the content of gaseous mixtures, since each gas has its own absorption characteristics, which differentiates it from other gases. The non-dispersive absorption of light in a gas is governed by the well-known Lambert-Beer law, which states that:

$$I = I_0 \cdot \exp \{ - [p] \cdot Y \cdot d \}$$

where I is the intensity of the transmitted light,

I_0 is the intensity of the incident light,

$[p]$ is the partial pressure of the gas absorbing the light,

d is the path length of the light in the gas, and

Y is the absorption coefficient per unit length, also known as the extinction coefficient.

It would therefore seem that a simple measurement of the transmission of light through a known length of the gas to be analyzed would be sufficient to determine its partial pressure or concentration. This is the basis of the technique known as non-dispersive infra-red spectroscopy, which is a primary method in use today for gas analysis, and a large volume of reference work is available on the subject.

The absorption phenomenon used for performing much NDIR spectroscopy, as it is known, is the absorption of light energy by gaseous molecules undergoing transitions between rotational-vibrational levels. The energy levels involved place these transitions in the infra-red region of the spectra. As an example, the absorption spectra of CO_2 molecules is centered in the 4.2 to 4.45 μm region, and in general, black body infra-red sources have been used for performing such measurements. Such black body sourced spectrometers have difficulty in differentiating between various isotopes of gases, since

there is only an extremely small shift in absorbed wavelength when an atom in a gas is replaced by a chemically identical isotopic atom. Since isotopic differentiation is becoming an increasingly important analytical tool, especially in such fields as breath tests in medical diagnostic testing, sensitive NDIR spectrometers capable of measuring changes in rare isotopic concentrations, are becoming important in the field of medical instrumentation and others.

In order to define the exact wavelength of the measurement, it is necessary to use some sort of filter with the black body, or a wavelength sensitive detector or source in order to define a narrow wavelength region where the absorption measurement takes place. In U. S. Patent No. 4,755,675 there is described a gas analyzer using a wavelength specific infra-red lamp source, based on a gas-filled discharge tube, which emits the characteristic spectral lines of the gas filling the lamp. By selecting the filling gas, it is possible to perform analysis of gas mixtures containing the gas used for the lamp fill. The authors even suggest that, being able to make use of such specific IR sources, an IR analyzer according to their invention would be capable of identifying and measuring the concentration of isotopically substituted "marker" molecules. However, the patent does not provide any explanation of how this can be performed in practice, and subsequent isotopic measurement prior art in this field has shown the complexity of the apparatus and method required for performing such analyses. Such lamps have been successfully used in capnography applications. However, for use in gas isotopic measurements, which require sensitivity and selectivity at least one order of magnitude higher than for capnographic measurements, the measurement and application techniques previously reported are totally inadequate.

Part of the complexity of gas isotope analysis arises because the Lambert-Beer law is only an approximation. In particular, the absorption coefficient Υ , is not a constant at all, but is dependent on a wide range of environmental factors, such as the analyzed gas pressure and temperature, the ambient humidity, the operating conditions of the light source, gas carriers both in the analyzed gas and in the source lamp gas, and short and long term changes in the lamp spectral characteristics. Many of the NDIR spectrometers described in the prior art have attempted to overcome this problem by using closely controlled environmental conditions, or frequent, complex calibration techniques, or a combination of both. Some examples of such prior art analyzers include the analyzer described by W. Fabinsky et al. in European Patent No. EP 0 584 897 A1,

that described by R. Grisaar et al. in U. S. Patent No. 5,146,294, and that described by Y. Kubo et al. in PCT Patent Application No. WO 97/14029.

All of the above described prior art analyzers appear to be complex, costly analytical instruments, which in most cases are also difficult to operate because of the rigorous and frequent calibration procedures required. To the best of the inventors' knowledge, no prior art gas analyzers exist which provide sufficient sensitivity and selectivity that enable them to be used for tests such as medical isotopic breath testing, and yet which are sufficiently compact, rugged and low cost, not requiring stable laboratory environments to enable them to become accepted for widespread use in the medical community.

SUMMARY OF THE INVENTION

The present invention seeks to provide an apparatus for analyzing the ratio of isotopic gases in a mixture containing two or more of such isotopes, which overcomes the drawbacks and disadvantages of prior art analyzers, and in particular, which provides analytic instrument performance standards in a compact, rugged and low cost instrument, operative outside the laboratory environment.

There is thus provided in accordance with a preferred embodiment of the present invention, an NDIR spectrometer based on the use of wavelength specific lamp sources, whose emission spectrum consists of discrete, narrow lines characteristic of the isotope present in the lamp, and which it is desired to measure with the spectrometer. This allows very high intrinsic sensitivity and very low cross sensitivity between the isotopes themselves and between the isotopes and other ambient gases in the operating environment, such as N_2O , whose absorption spectrum overlaps that of $^{13}\text{CO}_2$.

In addition, in order to reduce sensitivity to environmental changes, and to allow compact, rugged and low cost construction, and reliable and simple operation, without any calibration procedures, the NDIR spectrometer is constructed and operative with the reference and sample channels in close thermal and physical contact, and with the same pressure gas fill, such that both are affected in a similar manner by changes in environmental conditions. The reference gas channel therefore fully follows the physical,

electronic and environmental changes which occur in the whole system and accurately tracks changes in absorption due to these factors in the sample gas.

Furthermore, the signal detection and processing scheme is designed to extract the maximum resolution and accuracy in a ratio measurement of the isotopes, rather than in an absolute measurement. The electro-optical system is such that wherever possible, sources of drift in individual parallel components are eliminated by using single components operative for performing multiple functions. This is apparent in the various embodiments whereby a single detector with signal encoding is used to monitor more than one channel, or a single lamp is used to emit spectral lines from more than one isotope.

There is therefore provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer including an optical absorption analyzer for analyzing at least one isotope in a sample gas, the optical absorption analyzer including at least one wavelength-stable source of radiation which is specific to the at least one isotope.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the wavelength-stable source is a gas discharge source.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the analyzer determines the ratio of at least two isotopes in the sample gas.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the at least one wavelength-stable source of radiation comprises at least two wavelength-stable sources of radiation, each being specific to at least one isotope.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the at least one wavelength-stable source of radiation which is specific to at least one isotope is specific to two isotopes.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer including an optical absorption analyzer for analyzing the ratio of at least two isotopes in a sample gas, the optical absorption

analyzer including at least one wavelength-stable source of radiation which is specific to the at least one isotope.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer including an optical absorption analyzer for analyzing at least one isotope in a sample gas, the optical absorption analyzer including two wavelength-stable sources of radiation, each of which is specific to at least one isotope.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer including an optical absorption analyzer for analyzing at least one isotope in a sample gas, the optical absorption analyzer including at least one wavelength-stable source of radiation which is specific to two isotopes.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the optical absorption analyzer includes a reference gas channel, and wherein the sample gas is maintained under the same conditions as the reference gas.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the reference channel gas is a sample of the sample gas.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the reference channel gas is a mixture containing the at least one isotope at a known pressure and concentration.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the spectral overlap area is utilised by lowering the gas pressures.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer including at least first and second gas discharge lamps operated with respective first and second different timing characteristics, at least one detector viewing outputs of the at least first and second gas discharge lamps in the presence of gas to be analyzed, and a detection differentiator receiving an output from the at least one detector and distinguishing outputs corresponding to the first and second gas discharge lamps on the basis of the first and second different timing characteristics.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the first and second different timing characteristics are first and second frequencies.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the first and second different timing characteristics are first and second phases.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the at least one detector viewing outputs of the at least first and second gas discharge lamps in the presence of gas to be analyzed is a single detector.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the at least one detector viewing outputs of the at least first and second gas discharge lamps in the presence of gas to be analyzed are two detectors, each viewing one of first and second gas discharge lamps.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the least one detector viewing outputs of the at least first and second gas discharge lamps in the presence of gas to be analyzed are two detectors, one viewing absorption signal outputs from first and second gas discharge lamps and one viewing zero calibration from first and second gas discharge lamps.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the detection differentiator receiving an output from the at least one detector and distinguishing outputs corresponding to the first and second gas discharge lamps on the basis of the first and second different timing characteristics comprises first and second lock-in amplifiers.

There is therefore provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer including a discharge lamp containing at least first and second isotope labeled excitation gases, at least one detector viewing an output of the discharge lamp in the presence of gas to be analyzed, at least first and second filters corresponding to parts of respective first and second spectra of the at least first and second isotope labeled excitation gases, and a detection differentiator cooperating

with the detector for distinguishing detector outputs corresponding to the at least first and second spectra.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the detection differentiator comprises at least one light valve exposing the at least one detector to outputs of the first and second filters in accordance with a known timing sequence.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the at least one light valve exposing the at least one detector to outputs of the at least first and second filters in accordance with a known timing sequence is a chopper.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the at least one light valve exposing the at least one detector to outputs of the at least first and second filters in accordance with a known timing sequence is a spatial light modulator.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the at least one light valve is operated with respective first and second different timing characteristics and wherein the detection differentiator also comprises a detector output discriminator receiving an output from the detector and distinguishing outputs corresponding to the first and second excitation gases on the basis of the first and second different timing characteristics.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the first and second different timing characteristics are first and second frequencies.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the first and second different timing characteristics are first and second phases.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the detection differentiator comprises first and second lock-in amplifiers.

There is therefore provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer including a discharge lamp containing first and second isotope labeled excitation gases, first and second detectors each viewing an

output of the discharge lamp in the presence of gas to be analyzed, and first and second filters, each corresponding to a part of respective first and second spectra of the first and second isotope labeled excitation gases interposed between the discharge lamp and respective ones of the first and second detectors.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the filters are at least one of optical or gaseous filters.

There is therefore provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer including at least one gas discharge lamp containing at least first and second isotope labeled excitation gases having overlapping spectral ranges including at least some interdigitated spectral lines, a detector viewing outputs of the at least one gas discharge lamp in the presence of gas to be analyzed, and gas contents indicator receiving an output from the detector and employing information detected by the detector from at least two of the at least some interdigitated spectral lines.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the gas to be analyzed is maintained at a pressure below atmospheric pressure

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein filters are used to isolate non overlapping spectral ranges including at least some interdigitated spectral lines;

There is therefore provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer including an optical absorption analyzer for analyzing at least one isotope in a sample gas, the optical absorption analyzer including at least one wavelength-stable source of radiation which is specific to the at least one isotope, a channel containing a reference gas, and osmotic means for maintaining the sample gas and the reference gas at substantially the same partial pressure.

There is therefore provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer including an optical absorption analyzer for analyzing at least one isotope in a sample gas, the optical absorption analyzer including at least one wavelength-stable source of radiation which is specific to the at least one

isotope, a channel containing a reference gas, and pumping means for maintaining the sample gas and the reference gas at substantially the same partial pressure.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the gas analyzed is exhaled breath.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein only a selected part of the exhaled breath is used for the analyzing.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein an intermediate chamber is used to collect a plurality of breaths from at least part of the exhaled breath, and pumping means used for passing into analyzer.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the intermediate chamber has means to reduce its volume to drive out contents while maintaining substantially constant pressure.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the exhaled breath is continuously sampled by means of a connecting nasal cannula.

There is further provided in accordance with a preferred embodiment of the present invention, an isotopic gas analyzer as described above and wherein the exhaled breath is continuously sampled by means of a breathing tube.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be understood and appreciated more fully from the following detailed description, taken in conjunction with the drawings, in which:

Fig. 1 is a schematic view of an NDIR spectrometer according to a preferred embodiment of the present invention, showing the two separate isotope channels, each with their own lamp, absorption chambers, and fiber optical zero calibration channels, and with one common detector for all measurement channels.

Fig. 2 is an isometric view of the NDIR spectrometer shown in Fig. 1, showing the two separate frequency modulated isotope light sources, the four measurement channels, and a single detector.

Fig. 3 is an exploded plan view of the NDIR spectrometer shown in Fig. 2, showing how the constituent parts fit compactly together.

Fig. 4 is a cross sectional view of the NDIR spectrometer, showing the six measurement channels - the reference, sample and zero-calibration channels for each of the two isotopes.

Fig. 5 shows a preferred constructional method for the NDIR spectrometer, using extruded stainless steel pairs of tubes for the gas channels, embedded in a cast aluminum structure.

Fig. 6 is a functional cross sectional view of the NDIR spectrometer, showing how the two reference channels and the two sample channels are respectively pneumatically connected to each other by means of gas pipes, and the differential pressure measurement between them, and how the $^{13}\text{CO}_2$ and $^{12}\text{CO}_2$ chambers are connected thermally.

Fig. 7 is a schematic illustration of the shutter used to alternately measure the sample and reference channels.

Fig. 8 is a schematic view of the synchronous detection scheme used in the spectrophotometer described in Fig. 1, wherein each of the lamp sources is modulated at a different frequency, and four lock-in amplifiers are used for the four separate channels.

Fig. 9 shows the timing diagram and signal outputs for an alternative synchronous detection scheme, wherein both lamps are modulated at the same frequency by means of one or two RF exciters, and phase discrimination is used to differentiate between two separate isotope channels.

Figs. 10A to 10E show the timing diagrams which explain how the separate ^{12}C and ^{13}C signals are extracted electronically using the single lamp exciter scheme shown in Fig. 9.

Fig. 11 is a schematic view of an alternative NDIR spectrometer design, using two lamps as before, but with two separate detectors, one for each channel. The signal modulation is performed in this case using a rotary chopper to modulate the light.

Fig. 12 shows a chopper design suitable for use in the NDIR spectrometer shown in Fig. 11.

Fig. 13 is a representation of the three signals obtained from the reference, sample and zero calibration channels, using the chopper shown in Fig. 12.

Fig. 14 shows an alternative NDIR spectrometer design wherein only one lamp is used, this lamp being charged with a mixture of ^{12}C and ^{13}C such that it emits the spectra of both isotopes. Two detectors are used in this embodiment. Interference filters are used to discriminate between the two isotope channels.

Fig. 15 shows an NDIR spectrometer similar in design to that in Fig. 14, but using gas filters instead of interference filters.

Fig. 16 illustrates a further NDIR spectrometer design using only one lamp and one detector, wherein the light is switched alternately from each of the four channels to the detector by means of spatial light modulators.

Fig. 17 shows a possible arrangement of spatial light modulators for use in the embodiment shown in Fig. 16. The active elements shown are liquid crystals disposed between pairs of polarizers.

Fig. 18 shows a mechanical spatial chopper which can be used in the NDIR spectrometer embodiment shown in Fig. 16, as an alternative to electronic spatial light modulators. The chopper design shown is able to chop the light emerging from each of the five signal channels, two sample channels, two reference channels, and a zero calibration channel, at a different frequency, and thereby to discriminate between them in the single detector.

Fig. 19 is a representation of an osmotic system for ensuring that the partial pressure of the CO_2 in the sample chamber and the reference chamber are equal.

Fig. 20 is a representation of a pumped system for ensuring that the partial pressure of the CO_2 in the sample chamber and the reference chamber are close.

Fig. 21 illustrates how the pressure in the sample collection reservoir is maintained at a constant level while the sample gas is being accumulated or passed on after testing.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Reference is now made to Fig. 1 which shows a schematic view of the NDIR spectrometer of the breath analyzer, constructed and operative according to a

preferred embodiment of the present invention. (It should be noted that in all of the drawings, the symbols $^{12}\text{CO}_2$ and $^{13}\text{CO}_2$ have been abbreviated by the symbols 12C and 13C respectively.) This embodiment uses two lamps and one detector for the signal and reference channels, and a further detector for stabilizing the lamp outputs, as will be described below. The $^{13}\text{CO}_2$ chambers 10, both sample and reference, are considerably longer than the $^{12}\text{CO}_2$ chambers 11 in order to provide sufficient absorption signal from the small quantity of $^{13}\text{CO}_2$ present in the sample gas.

The IR lamps 12 are gas discharge lamps as described in U. S. Patent 5,300,859. Each of them is filled with an essentially pure filling of the isotopic gas, either $^{13}\text{CO}_2$ or $^{12}\text{CO}_2$. As a result, each lamp emits a radiation spectrum substantially of the appropriate isotope only. The lamps are each modulated at a different frequency, by means of modulating the RF exciter power supply to each lamp. By this means, the separate frequency components of the combined signal appearing on the single signal detector can be separated by means of synchronous detection techniques, as will be explained below.

However, the highest level of $^{13}\text{CO}_2$ enrichment available is about 99.3%, which means that the $^{13}\text{CO}_2$ lamp spectrum still contains a small percentage of $^{12}\text{CO}_2$ spectral lines. In fact, the situation is more serious than the percentage enrichment implies, since the remaining 0.7% of $^{12}\text{CO}_2$ produces several times that level of $^{12}\text{CO}_2$ spectral lines, because of interaction effects in the gas discharge. Since the sample breath analysis has to detect very small changes in the $^{13}\text{CO}_2 / ^{12}\text{CO}_2$ ratio, and since the percentage of $^{13}\text{CO}_2$ is so much smaller than that of $^{12}\text{CO}_2$, even a small residue of $^{12}\text{CO}_2$ lines in the incident light will seriously affect the accuracy of the measurement. For this reason, an absorbing filter filled with $^{12}\text{CO}_2$ gas is placed in the $^{13}\text{CO}_2$ channel, so as to effectively absorb all of the remaining $^{12}\text{CO}_2$ lines in the $^{13}\text{CO}_2$ source. As an alternative, an optical bandpass filter 13 can be used for filtering out the interfering spectral lines as explained above. Another possible reason for the use of filters is to remove part of the emission. Part of the emission is removed in such a way that light passing through the 13C channel cannot be absorbed by the 12C and vice versa. This addresses the problem of cross sensitivity. Another approach to address this problem is to lower the pressure to avoid absorption of the 13C light by the broad absorption line of 12C at atmospheric pressure.

To follow short term fluctuations in lamp intensity, it may be necessary to monitor the light output from each lamp constantly and the level used for correcting the

measured absorption in the sample channels. The luminous output from each lamp is therefore sampled by means of optical fibers 14. These signals are measured on the calibration detector 15, and the output used as a reference signal for normalizing the sample signals to a constant level. Although both fibers go to one detector, since the optical signal on each fiber is modulated at a different frequency, depending on the modulation frequencies of the two lamps, the two signals can be separated by means of standard synchronous detection techniques. This procedure overcomes the problem of lamp intensity drift in this embodiment, which uses two separate lamps for each isotope.

The sample detector 16 is preferably a PbSe infra-red detector, which is cooled by means of a one or two stage thermoelectric cooler to between -10°C to -50°C . This is done to improve the sensitivity, stability and noise performance of the detector at the CO_2 wavelengths in the region of 4.2 to $4.45\mu\text{m}$. In spite of cooling the detectors to a fixed and low temperature, they still exhibit some drift with time, both electrically and thermally. However, since the measurement is done on ratios of channels, the effects of this drift tend to be complementary, and it is not a major source of inaccuracy in this embodiment of the breath test system.

Fig. 2 shows an isometric view of the NDIR spectrometer. The compact construction of this embodiment is clear from this drawing. The analysis chambers are built into a block of aluminum 21. The $^{13}\text{CO}_2$ chambers 22, both sample and reference, are considerably longer than the $^{12}\text{CO}_2$ chambers 23 as explained above. The four absorption chambers sample and reference for each of the two isotopes are visible in the end plate 24 of the analyzer block. A thin steel shutter 25 slides along a thin recess in the end plate for switching the measurement between the reference channel and the sample gas channel. This is done approximately every 10 to 60 secs, depending on the measurement situation encountered. This time is taken as a compromise between the need to perform averaging over a sufficiently long time to obtain a stable and representative signal, and the need to perform the reference and sample measurements sufficiently close in time that the system conditions do not change appreciably between measurements. The axes of the isotope lamps 26 and the absorption chambers 22, 23 are aligned such that the output light beams from the four channels are all directed into the single detector 28 by means of the light cone 27.

Fig. 3 shows an exploded cut-away view of the spectrometer shown in Fig. 1 and Fig. 2. The chamber block 30, isotope lamps 31 32, shutter 33, light cone 37 and the

detector cover 34 are shown. The gas inlet 35 and outlet 36 to the sample chamber are positioned in the side of the block, and the gases led to their respective chambers by means of internal passages drilled into the aluminum block.

Fig. 4 shows a cut-away cross section of the absorption chambers of the NDIR spectrometer shown in Figs. 1 to 3. The two reference absorption chambers 41 42, are connected together pneumatically by means of a tube 43, so that the sample and reference channels contain the same gas at the same pressure. The sample absorption chambers 44 45 are similarly connected by means of tube 46. In addition, both the $^{13}\text{CO}_2$ and the $^{12}\text{CO}_2$ channels of the NDIR spectrometer are thermally strapped together by means of a thick shunt of conductive metal 47, such that the gases in both isotopic channels are thermally as close as possible to being in equilibrium. This feature assists in attaining good thermal stability to the measuring system. The optical fibers 48 which monitor the lamp 49 intensities are located such that they do not interfere with the entry of the lamp light to the analysis chambers.

Fig. 5 shows the materials and method of construction of NDIR spectrometer absorption chambers according to a preferred embodiment of the present invention. The materials have been selected to provide compactness with high strength and low cost construction. The absorption chambers are constructed of an extruded section of a pair of stainless steel tubes 52. The whole assembly, with the fiber optical monitor fibers 54, is mounted inside a light aluminum profile structure 56, which provides mechanical stability together with low cost and low weight.

Fig. 6 is a view taken from the front of the gas channels, showing the $^{13}\text{CO}_2$ filter 62 located in front of the $^{13}\text{CO}_2$ gas channels, and the $^{12}\text{CO}_2$ filter 64 located in front of the $^{12}\text{CO}_2$ channels. These filters function to remove unnecessary emission regions from the lamp, and to prevent thermal background emission from reaching the detector. A high sensitivity differential pressure sensor 66 is connected between reference and sample channels. It is used to ensure that the pressure in the reference and sample channels, both being at a pressure lower than atmospheric, are equated. In addition, the reference channel also includes an absolute pressure sensor, for monitoring the attainment of the reduced pressure required to achieve good measurement sensitivity.

Fig. 7 illustrates how the shutter 72 is used to select the measurement channel in use. At the beginning of each sample measurement, the shutter is in the lower position, thereby allowing the lamps to illuminate the reference channels, and to obtain a baseline

reference measurement. This measurement is a monitor to environmental changes taking place in the system, changes in the lamp light spectrum, changes in filter characteristics, or in detectors or electronics characteristics, all of which should be fairly constant. If the reference measurement does show change, a correction factor is used to compensate the sample channel readings for the change in environmental conditions. After completion of the reference measurement, the shutter is moved up into the position shown in the drawing, and the sample measurement taken from the sample channels. Once this sample measurement has been obtained with sufficient accuracy, the sample is removed pneumatically, and the analyzer ready for receiving its next measurement sample. The chamber purging and the conditioning of the next sample is executed during the reference measurement. This is performed approximately once per minute.

Fig. 8 is a schematic view of the electronic method whereby signals from the four absorption channels can be discriminated. The $^{13}\text{CO}_2$ lamp is modulated at frequency ω_1 , while the $^{12}\text{CO}_2$ lamp is modulated at frequency ω_2 . Each channel, sample and zero reference, has its own detector 82 84 respectively. Four lock-in amplifier channels 86 are required to extract the four modulated signals from the sample and reference channels of the two isotopic lamps. The trigger signals for each of these lock-in amplifiers, is taken from the driver signals of the lamp source modulation power supply. Modulation frequencies are in the range of 1 to 200 Hz, with 70 Hz. being a typical value.

It is also possible to modulate both lamps at the same frequency, either using one RF exciter switched between the two lamps, or using two exciters switched on and off in antiphase, and to use phase information in order to discriminate between the two signals from each lamp. This is illustrated in Fig 9, which shows a continuous train of modulating pulses 92 applied alternately to each lamp, and the resulting train of alternating signals 94 on the detector. An instrument such as a box-car integrator is used to extract the signal from each isotopic lamp separately. This detection scheme has an advantage in that there is less sensitivity to drift in exciter output, and that there is no electronic cross sensitivity between the two isotopic lamps, since each is separated in time, and not in frequency.

The method whereby the two different isotopic channels are separated electronically, when using the single exciter modulation scheme shown in Fig. 9, is illustrated in Figs. 10A to 10E. Fig. 10A represents the continuous stream of square wave pulses, which are alternately directed to the $^{13}\text{CO}_2$ lamp or the $^{12}\text{CO}_2$ lamp, as

shown in Figs. 10B and 10C respectively. These pulse trains are convoluted with the output signals from the detector, and the resulting outputs are respectively a train of $^{13}\text{CO}_2$ pulses as shown in Fig. 10D, or a train of $^{12}\text{CO}_2$ pulses as shown in Fig. 10E. The convolution is performed by a box-car integrator, or a phase sensitive detector.

A further preferred embodiment of the present invention is shown in Fig. 11. As previously, two lamps are used, one for each isotope ^{12}C ^{14}C . Each isotope has its own complete measuring system, with sample, reference and calibration channels, connected only by means of the mechanical, thermal and pneumatic connections as previously described. In order to reduce the effects of detector drift, one detector is used for all three signals in each isotope measurement channel. In order that each detector can differentiate between the three types of signal received from its light source, a mechanical chopper 116 is used. The chopper can differentiate between the three channels either by means of frequency discrimination, or by means of phase discrimination. In the former case, the chopper has three sets of holes, each set at a different radial distance from the center, and each set having a different number of holes. In this way, three different frequencies for different spatial regions of the source lamp are defined, where these three regions correspond to the three different channels. If phase discrimination is used, the chopper has three rows of slots, each at different radial distance corresponding to the location of the three channels, and with the sets of slots arranged at fixed angular intervals around the chopper. A chopper for use in phase discrimination is shown in Fig. 12. In Fig. 13, the signal received at the detector of either isotope channel when using such a chopper, is shown as a function of time.

There are a number of disadvantages of frequency discrimination choppers when compared to phase discrimination choppers. The first problem is that it is very difficult to provide a phase sensitive detector with a sufficiently high selectivity for the discrimination required by the present system. If the selectivity of the phase sensitive detector is insufficient, enough of the signal of the unwanted frequency will be detected to render the measurement inaccurate. In order to provide good detection accuracy for the $^{13}\text{CO}_2$ in the sample breath, a selectivity of 1 : 20,000 is required, which is difficult to achieve.

Furthermore, an electronic cross sensitivity effect is present in the detectors, which may have a non-linear response at the upper and lower extremities of their range. Therefore, if a strong signal is present at one frequency, it may shift the operating point

of the detector in such a way that it behaves non-linearly to a weak signal of a different frequency imposed upon it. This would severely affect the measurement accuracy.

On the other hand, there is also a disadvantage to phase discrimination choppers. Only one channel can be open at any one time, unlike frequency discrimination choppers, wherein all the channels can be transmissive at any time, all being at different frequencies. Consequently, the phase discrimination method has a lower duty ratio, and therefore a less sensitive detection capability.

Both of the above embodiments according to the present invention, use two lamps, and calibration detectors are used to eliminate the effects of source lamp variation, as described above.

Fig. 14 and 15 show preferred embodiments of an NDIR spectrometer constructed and operative according to the present invention, wherein only one lamp source is used. The lamp 142 is filled with a mixture of the two isotopes whose ratio is to be measured, in this embodiment $^{13}\text{CO}_2$ and $^{12}\text{CO}_2$. Since only one lamp is being used, changes in operating conditions or environmental effects, take place in both channels simultaneously, and therefore have greatly reduced effects on the measurement accuracy. In both of the Figs. 14 and 15, the light from the lamp source of the NDIR spectrometer is collected and collimated into two separate beams by means of an entry lens 144. Each beam then passes through its relevant absorption chambers, and via the wavelength filters 146 to the detectors. These may be separate detectors, or preferably, parts of one larger pixelated detector, in which case detector drift will be reduced. In the embodiment of Fig. 14, optical interference filters are used for filtering out the unwanted spectral lines from the light in each isotope channel, while in Fig. 15, gas filters 152 are used. A combination of gas and optical filters can be used. Signal modulation is performed using a mechanical chopper operating either in the frequency or the phase chopping mode, or by means of modulating the lamp and synchronously detecting the signal on each detector separately, while switching between the reference and sample channels by means of a shutter.

A further embodiment of the present invention is shown in Fig. 16. In this embodiment, a further reduction in the sensitivity of the system to external and environmental conditions is achieved by the use of only one detector 162 for both isotope channels, instead of the two used in all of the previous embodiments. The one

lamp - one detector embodiment represents the system with the best environmental stability with respect to component drift.

In general light valves may be used in gas absorption measurements wherein a light source cannot be modulated internally or cannot be modulated fast enough, or wherein more than one channel is viewed by one detector, or wherein the number of channels monitored is lower than the number of detectors. In particular, in this application, discrimination between the signals from the five separate channels - two reference, two sample and one lamp level calibration signal - is achieved by means of an SLM, a spatial light modulator 164. Such a spatial light modulator can preferably be a liquid crystal matrix placed between polarizers, or a DMD (Digital Mirror Device) pixelated mirror, such as those produced by Texas Instruments Inc. of Houston, Texas, or a deflecting membrane device, such as produced by Optron Inc, or an active reflecting device such as those produced by A.T.&T. The function of the spatial light modulator is to modulate the light from each channel at a different phase or frequency, according to a predetermined sequence and frequency. This sequence and frequency is conveyed to the phase sensitive detector used to discriminate between the various signals, in order to extract the signal information relevant to each measurement channel. The SLM can be operated at high frequency, thereby reducing the noise contribution to the signal. The use of an SLM, wherein effectively avoids the problem mentioned previously of the limited selectivity of phase sensitive detectors, since very widely differing frequencies of modulation with negligible electric cross sensitivity can be used.

Fig. 17 illustrates a preferred embodiment of such an SLM, using transmission liquid crystal elements 172. The light from the reference and sample chambers for each isotope channel is passed through a polarizer 174, where it attains a linear direction of polarization. If a particular liquid crystal element 172 is activated, the light passing through that element will attain a polarization switched by a further 90°, so that on passage through another polarizing element 176, the light is cut off. In this way, each liquid crystal element acts as a fast electrically operated switch.

It is also possible to use a mechanical chopper instead of an SLM for spatially switching the various signal channels into the detector. Fig. 18 is a schematic example of such a chopper. Each row of holes 182 is located at a radius from the center such that each row falls exactly on the location 184 of one of the five optical signal channels, labeled ω_1 to ω_5 . In Fig. 18, the optical signal channels are shown schematically in one

straight line for simplicity, whereas in a real embodiment, they will be staggered to fall in their correct geometrical location in the NDIR spectrometer. The frequencies are chosen such that there are no low order common harmonics between them, and the further apart the frequencies, the better the discrimination. In this case, the system may be constructed to generate a phase difference as in Fig. 12.

Fig. 19 and 20 show two alternative preferred embodiments for ensuring that the partial pressure of the CO_2 in the sample chamber and the reference chamber are close, in order to ensure that the $^{13}\text{CO}_2$ absorption is measured accurately and under close conditions in both chambers. The embodiments described are of a breath test analyzer application, this being one of the common uses of isotopic gaseous analysis of CO_2 , but the construction and methods shown are applicable to any isotopic gas analysis.

In the embodiment shown in Fig. 19, the sample breaths are exhaled into a reservoir 192, which is connected to the sample absorption measurement chamber by means of a membrane 194 permeable to CO_2 . The sample chamber 196 is initially filled with an inert background gas such as pure nitrogen at atmospheric pressure. The reference chamber 198 is filled either with the first breath sample, or with a predetermined reference gas mixture. The CO_2 from the reservoir diffuses into the sample chamber until the $^{12}\text{CO}_2$ partial pressure as determined by the $^{12}\text{CO}_2$ absorption measurement itself, is equal in the sample and reference chambers. When this point is reached, the membrane passage is sealed off by valving means, and the $^{13}\text{CO}_2$ measurement is performed accurately in the knowledge that the same conditions exist in the sample and reference chambers.

Fig. 20 illustrates another preferred embodiment in which the partial pressure of the CO_2 in the sample chamber and the reference chamber are equalized. As in the embodiment shown in Fig. 19, the sample breaths are exhaled into a reservoir 200. This reservoir is connected by means of a pump 202 to the sample chamber 204, which, as in the embodiment of Fig. 19, is initially filled with an inert background gas such as pure nitrogen at atmospheric pressure. The pump is operated until the $^{12}\text{CO}_2$ partial pressures, as determined by the $^{12}\text{CO}_2$ absorption measurement itself, in the sample and reference chambers are close to each other. When this point is reached, the pump is turned off, and the $^{13}\text{CO}_2$ measurement is performed accurately in the knowledge that close conditions exist in the sample and reference 206 chambers. The condition of equal absorption is also monitored by means of an absolute 209 and a differential pressure

measurement gauge 208. The pressure measurement is required to correct for changes in the extinction coefficient Υ with pressure. As a result of these changes, the same absorption is obtained at different partial pressures. This procedure is likely to result in incorrect isotopic ratio measurements, unless an appropriate correction is applied, which has to be determined by control experiments.

Fig. 21 shows the gas handling equipment used in a preferred embodiment of the present invention in order to ensure that the sample reservoir is maintained at a constant pressure while sample gas is being accumulated or pumped into the testing chamber. Entry of breath is permitted by opening of the one-way solenoid valve 210. The sample reservoir 212 is fitted with a piston 216, open on its other side to atmospheric pressure, such that the reservoir fills up naturally. At the exit from the reservoir, the two-way solenoid valve 214 is used to enable the accumulated sample to be pumped into the sample chamber. When this takes place, the piston falls, maintaining constant pressure in the vacated volume, such that no vacuum is formed.

The use of a reservoir in the embodiments shown in Figs. 19 and 20 allows the analyzer to perform sampling of the exhaled breathes in such a way as to substantially increase the reliability of the measurement procedure. Firstly, it is known that exhaled breath follows a characteristic CO_2 wave front, whereby there is an initial steep rise in the CO_2 concentration of each exhaled breath, until a slowly rising plateau is reached. At the end of the breath, the volume falls rapidly again to a very low residual level. In order to ensure that the breath sampled is characteristic of the breath exhaled from the lungs, and not breath which has been standing in the oral or nasal passages, or has been reinhaled from a previous breath, it is important to sample breath only from the plateau region of the breath wave. This can be easily accomplished according to the embodiment described herein using a sampling reservoir, by means of valving which rejects the breath from the first and last part of each breath wave, and only samples breath from the plateau region. The detection of the exhalation can be performed optically by following changes in the optical absorption of the exhaled gas, or by monitoring changes in the exhalation dynamic pressure.

Furthermore, the use of such a sampling reservoir allows the analyzer to take an average of several breaths, instead of relying on a single breath sample, which could be atypical of the mean breath of the patient. The partial pressures of the various components of exhaled breath vary from breath to breath in a random manner, and

averaging is therefore a very important procedure to ensure accurate measurements. The patient exhales a number of breaths freely into the reservoir. From the reservoir, the analyzer draws an averaged sample for measurement once measurement of the previous sample has been completed. This embodiment has a number of additional advantages. Firstly, the patient is non-functional in the sampling process, and simply breathes at his natural rate into the breath tube, or via a nasal cannula. The inlet valving of the analyzer ensures that the correct sample is taken for measurement. In addition, the breath is allowed to stand, which ensures good temperature and pressure conditioning with respect to the environment. Finally, the sampling from the reservoir is performed at an approximately fixed partial pressure, such that the measurement is less sensitive to environmental and lamp emission changes, and to cross sensitivity.

It will be appreciated by persons skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather the scope of the present invention includes both combinations and subcombinations of various features described hereinabove as well as variations and modifications thereto which would occur to a person of skill in the art upon reading the above description and which are not in the prior art.

CLAIMS

We claim:

1. An isotopic gas analyzer comprising:
an optical absorption analyzer for analyzing at least one isotope in a sample gas, said optical absorption analyzer including at least one wavelength-stable source of radiation which is specific to said at least one isotope.
2. An isotopic gas analyzer according to claim 1 and wherein said wavelength-stable source is a gas discharge source.
3. An isotopic gas analyzer according to either of the previous claims, and wherein said analyzer determines the ratio of at least two isotopes in said sample gas.
4. An isotopic gas analyzer according to any of the previous claims, and wherein said at least one wavelength-stable source of radiation comprises at least two wavelength-stable sources of radiation, each being specific to at least one isotope.
5. An isotopic gas analyzer according to any of the previous claims, and wherein said at least one wavelength-stable source of radiation which is specific to at least one isotope is specific to two isotopes.
6. An isotopic gas analyzer comprising:
an optical absorption analyzer for analyzing the ratio of at least two isotopes in a sample gas, said optical absorption analyzer including at least one wavelength-stable source of radiation which is specific to said at least one isotope.
7. An isotopic gas analyzer comprising:
an optical absorption analyzer for analyzing at least one isotope in a sample gas, said optical absorption analyzer including two wavelength-stable sources of radiation, each of which is specific to at least one isotope.

8. An isotopic gas analyzer comprising:
an optical absorption analyzer for analyzing at least one isotope in a sample gas, said optical absorption analyzer including at least one wavelength-stable source of radiation which is specific to two isotopes.
9. An isotopic gas analyzer according to claim 1 and wherein said optical absorption analyzer includes a reference gas channel, and wherein said sample gas is maintained under the same conditions as reference gas.
10. An isotopic gas analyzer according to claim 9 and wherein said reference channel gas is a sample of said sample gas.
11. An isotopic gas analyzer according to claim 9 and wherein said reference channel gas is a mixture containing said at least one isotope at a known pressure and concentration.
12. An isotopic gas analyzer according to claim 9 and wherein the spectral overlap area is utilised by lowering the gas pressures.
13. An isotopic gas analyzer comprising:
at least first and second gas discharge lamps operated with respective first and second different timing characteristics;
at least one detector viewing outputs of said at least first and second gas discharge lamps in the presence of gas to be analyzed; and
a detection differentiator receiving an output from said at least one detector and distinguishing outputs corresponding to the first and second gas discharge lamps on the basis of said first and second different timing characteristics.
14. An isotopic gas analyzer according to claim 13 and wherein said first and second different timing characteristics are first and second frequencies.

15. An isotopic gas analyzer according to claim 13 and wherein said first and second different timing characteristics are first and second phases.
16. An isotopic gas analyzer according to claim 13 and wherein said at least one detector viewing outputs of said at least first and second gas discharge lamps in the presence of gas to be analyzed is a single detector.
17. An isotopic gas analyzer according to claim 13 and wherein said at least one detector viewing outputs of said at least first and second gas discharge lamps in the presence of gas to be analyzed are two detectors, each viewing one of first and second gas discharge lamps.
18. An isotopic gas analyzer according to claim 13 and wherein said at least one detector viewing outputs of said at least first and second gas discharge lamps in the presence of gas to be analyzed are two detectors, one viewing absorption signal outputs from first and second gas discharge lamps and one viewing zero calibration from first and second gas discharge lamps.
19. An isotopic gas analyzer according to claim 13 and wherein said detection differentiator receiving an output from said at least one detector and distinguishing outputs corresponding to the first and second gas discharge lamps on the basis of said first and second different timing characteristics comprises first and second lock-in amplifiers.
20. An isotopic gas analyzer comprising:
- a discharge lamp containing at least first and second isotope labeled excitation gases;
 - at least one detector viewing an output of said discharge lamp in the presence of gas to be analyzed;
 - at least first and second filters corresponding to parts of respective first and second spectra of said at least first and second isotope labeled excitation gases; and
 - a detection differentiator cooperating with the detector for distinguishing detector outputs corresponding to said at least first and second spectra.

21. An isotopic gas analyzer according to any of the previous claims, and wherein the detection differentiator comprises at least one light valve exposing said at least one detector to outputs of said first and second filters in accordance with a known timing sequence.
22. An isotopic gas analyzer according to claim 21 and wherein said at least one light valve exposing said at least one detector to outputs of said at least first and second filters in accordance with a known timing sequence is a chopper.
23. An isotopic gas analyzer according to claim 21 and wherein said at least one light valve exposing said at least one detector to outputs of said at least first and second filters in accordance with a known timing sequence is a spatial light modulator.
24. An isotopic gas analyzer according to claim 21 and wherein the at least one light valve is operated with respective first and second different timing characteristics and wherein the detection differentiator also comprises a detector output discriminator receiving an output from said detector and distinguishing outputs corresponding to the first and second excitation gases on the basis of said first and second different timing characteristics.
25. An isotopic gas analyzer according to claim 24 and wherein said first and second different timing characteristics are first and second frequencies.
26. An isotopic gas analyzer according to claim 24 and wherein said first and second different timing characteristics are first and second phases.
27. An isotopic gas analyzer according to claim 24 and wherein said detection differentiator comprises first and second lock-in amplifiers.

28. An isotopic gas analyzer comprising:
a discharge lamp containing first and second isotope labeled excitation gases;
first and second detectors each viewing an output of said discharge lamp in the presence of gas to be analyzed; and
first and second filters, each corresponding to a part of respective first and second spectra of said first and second isotope labeled excitation gases interposed between said discharge lamp and respective ones of said first and second detectors.
29. An isotopic gas analyzer according to any of the previous claims 20 to 28, and wherein said filters are at least one of optical or gaseous filters.
30. An isotopic gas analyzer comprising:
at least one gas discharge lamp containing at least first and second isotope labeled excitation gases having overlapping spectral ranges including at least some interdigitated spectral lines;
a detector viewing outputs of said at least one gas discharge lamp in the presence of gas to be analyzed; and
a gas contents indicator receiving an output from said detector and employing information detected by said detector from at least two of said at least some interdigitated spectral lines.
31. An isotopic gas analyzer according to claim 30 and wherein said gas to be analyzed is maintained at a pressure below atmospheric pressure
32. An isotopic gas analyzer according to claim 30 and wherein filters are used to isolate non overlapping spectral ranges including at least some interdigitated spectral lines;
33. An isotopic gas analyzer comprising:
an optical absorption analyzer for analyzing at least one isotope in a sample gas, said optical absorption analyzer including at least one wavelength-stable source of radiation which is specific to said at least one isotope;

a channel containing a reference gas; and
osmotic means for maintaining said sample gas and said reference gas at substantially the same partial pressure.

34. An isotopic gas analyzer comprising:

an optical absorption analyzer for analyzing at least one isotope in a sample gas, said optical absorption analyzer including at least one wavelength-stable source of radiation which is specific to said at least one isotope;

a channel containing a reference gas; and

pumping means for maintaining said sample gas and said reference gas at substantially the same partial pressure.

35. An isotopic gas analyser according to any of the previous claims and wherein the gas analyzed is exhaled breath.

36. An isotopic gas analyser according to claim 35 and wherein only a selected part of said exhaled breath is used for said analyzing.

37. An isotopic gas analyser according to claim 35 and wherein an intermediate chamber is used to collect a plurality of breaths from at least part of said exhaled breath, and pumping means used for passing into analyzer.

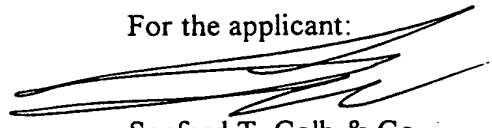
38. An isotopic gas analyser according to claim 37 and wherein said intermediate chamber has means to reduce its volume to drive out contents while maintaining substantially constant pressure.

39. An isotopic gas analyser according to claim 35 and wherein said exhaled breath is continuously sampled by means of a connecting nasal cannula.

40. An isotopic gas analyser according to claim 35 and wherein said exhaled breath is continuously sampled by means of a breathing tube.

41. Apparatus substantially as shown and described hereinabove.
42. Apparatus substantially as illustrated in any of the drawings.

For the applicant:

A handwritten signature in black ink, appearing to be "Sanford T. Colb", written over a horizontal line.

Sanford T. Colb & Co.,
Advocates & Patent Attorneys
C: 28519

FIG. 1

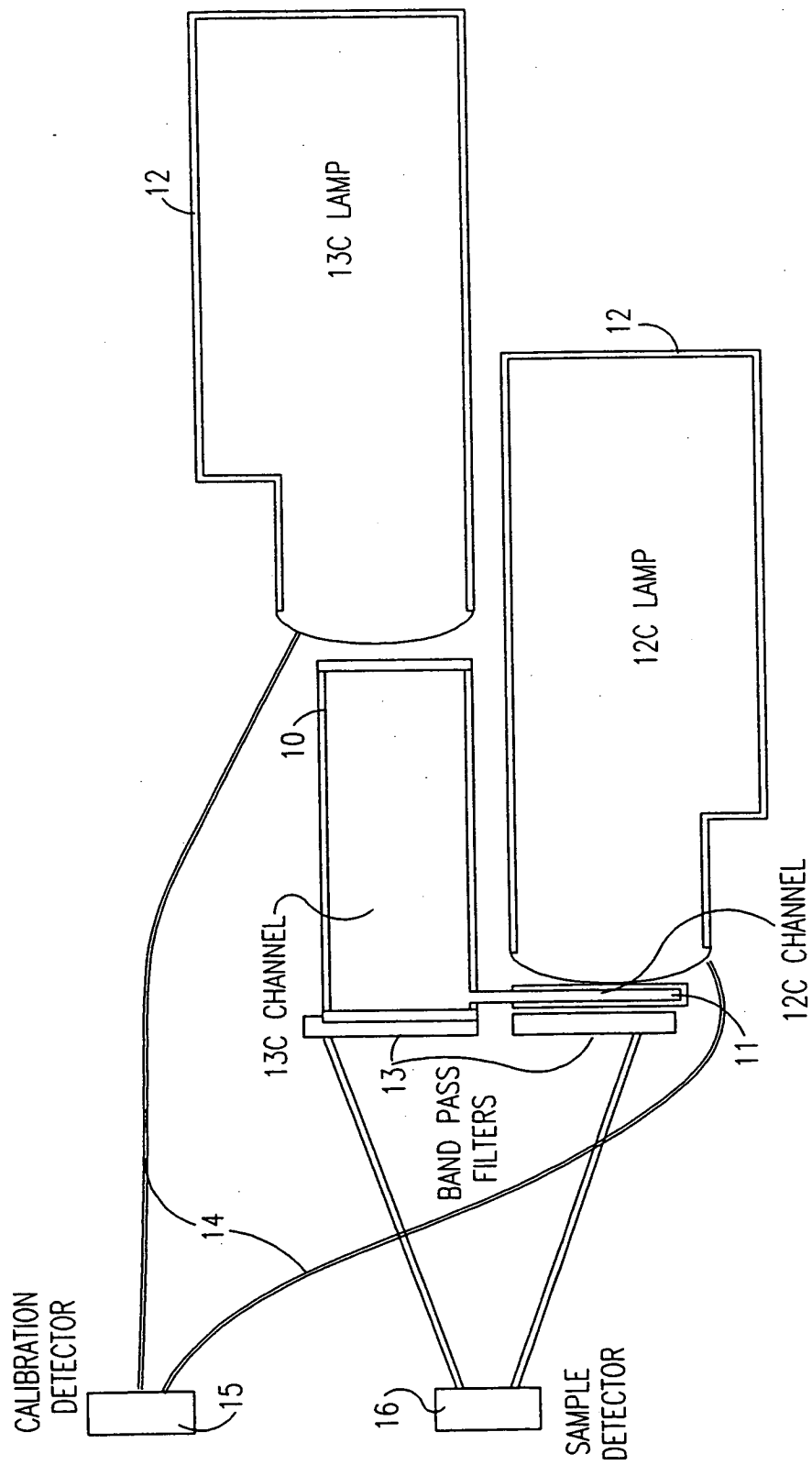


FIG. 3

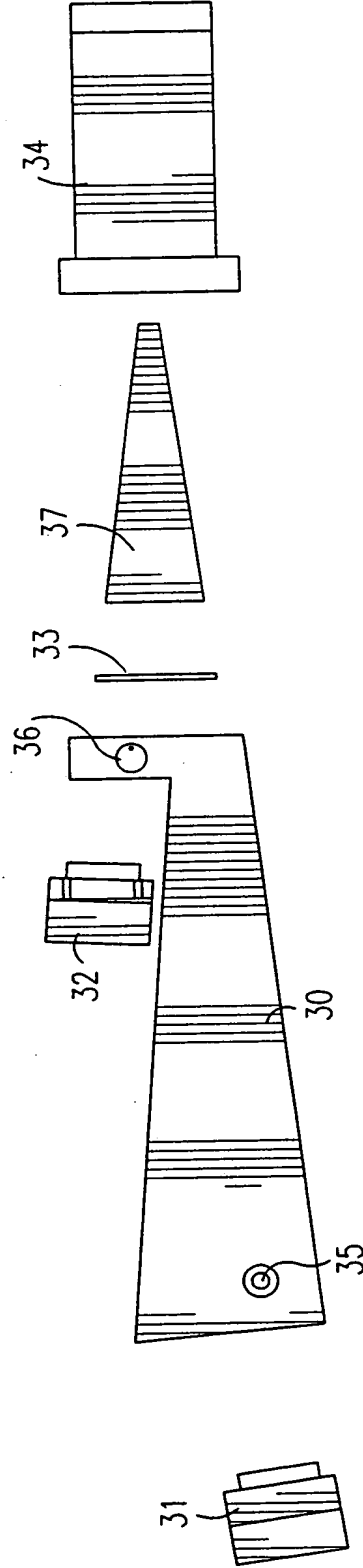


FIG. 4

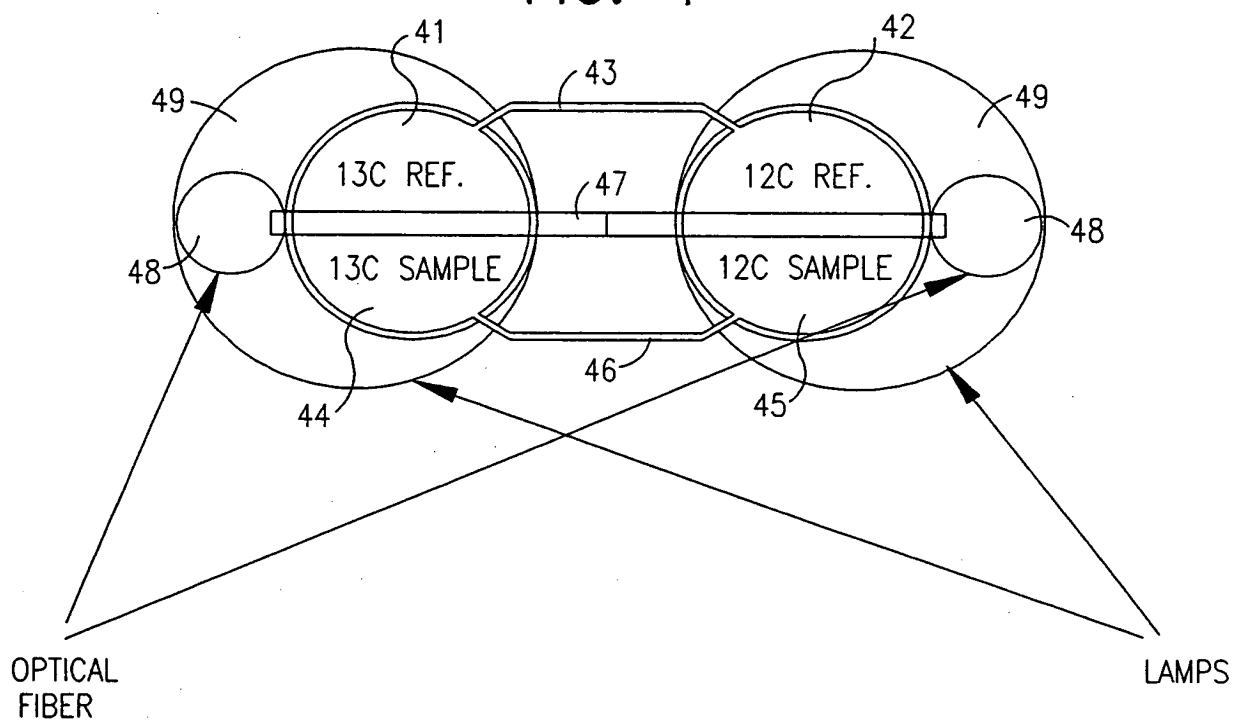


FIG. 5

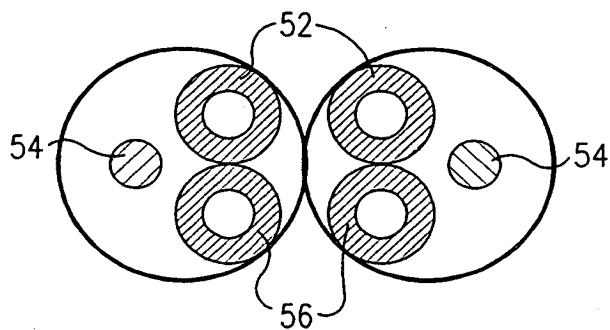


FIG. 6

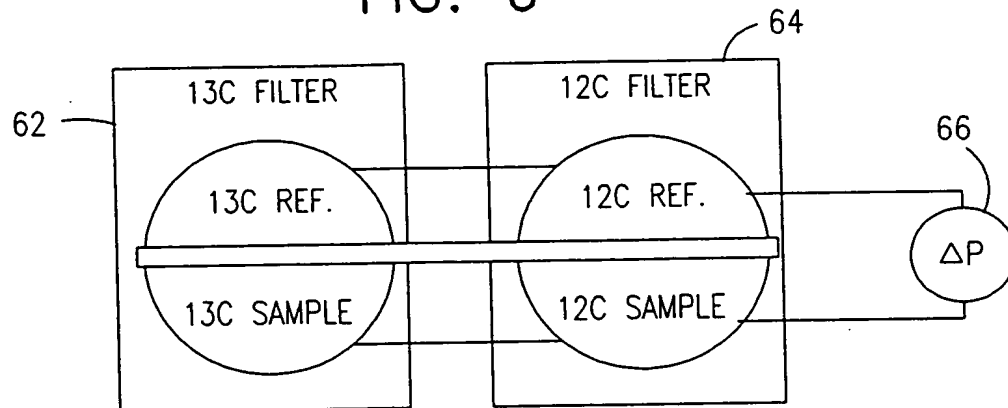


FIG. 7

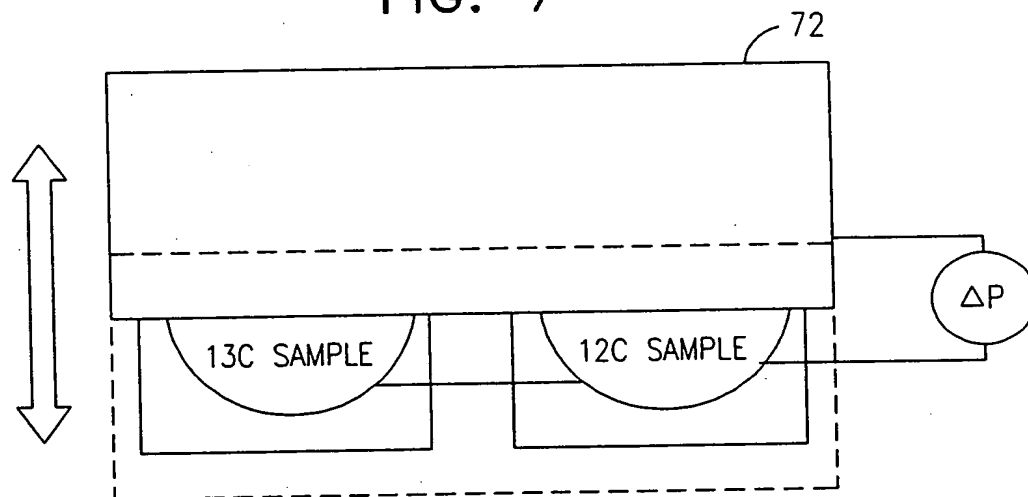
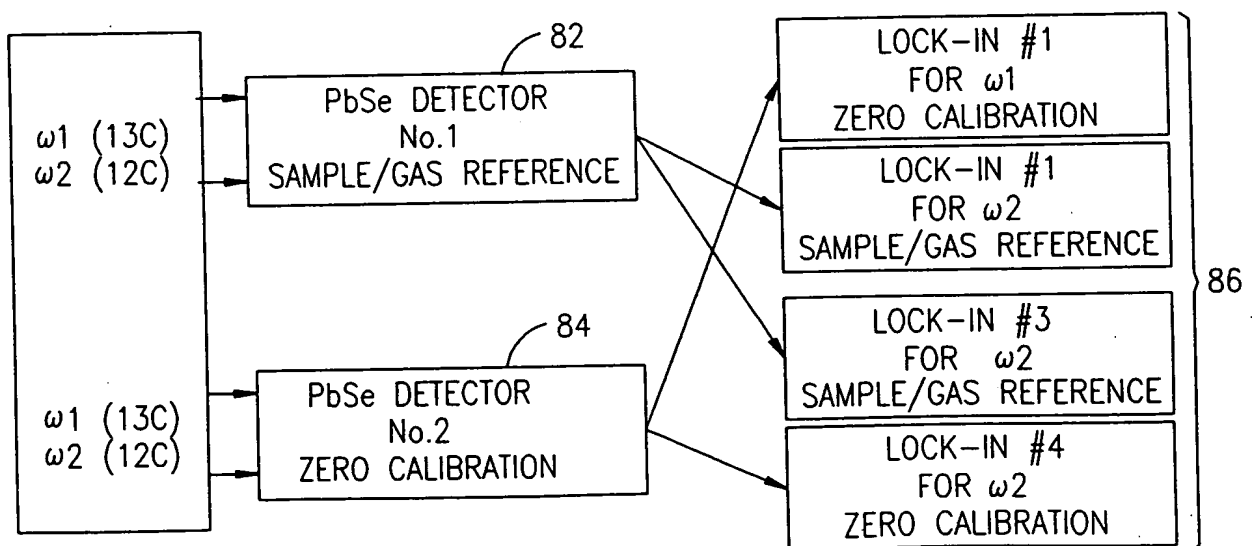


FIG. 8



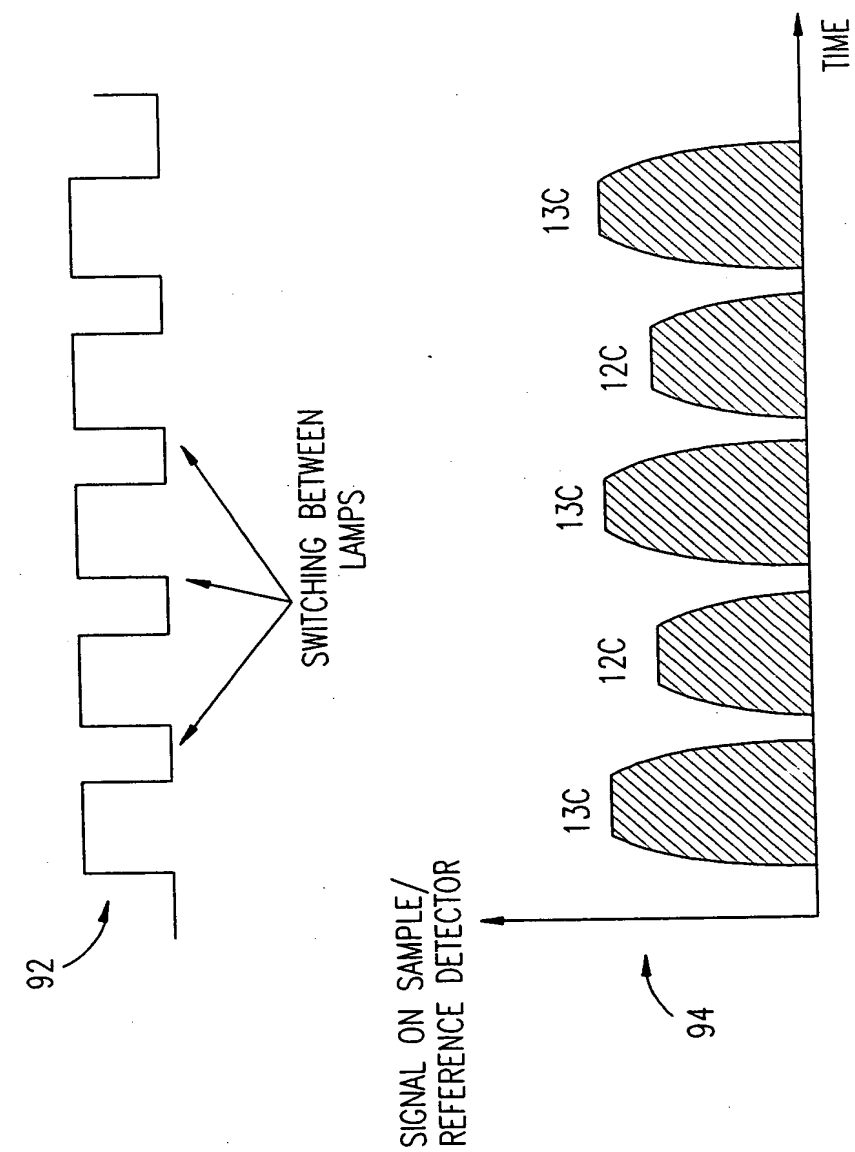


FIG. 9

FIG. 10A

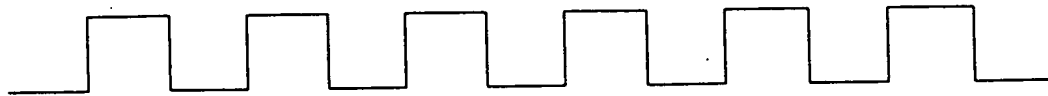


FIG. 10B

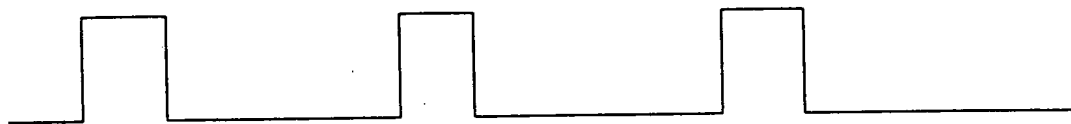
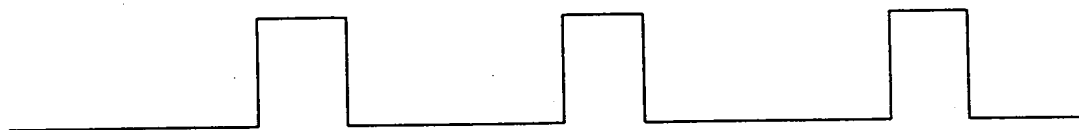
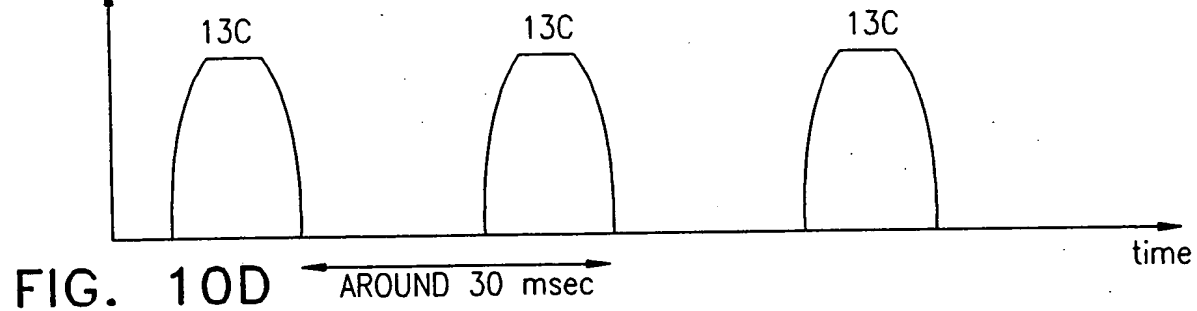


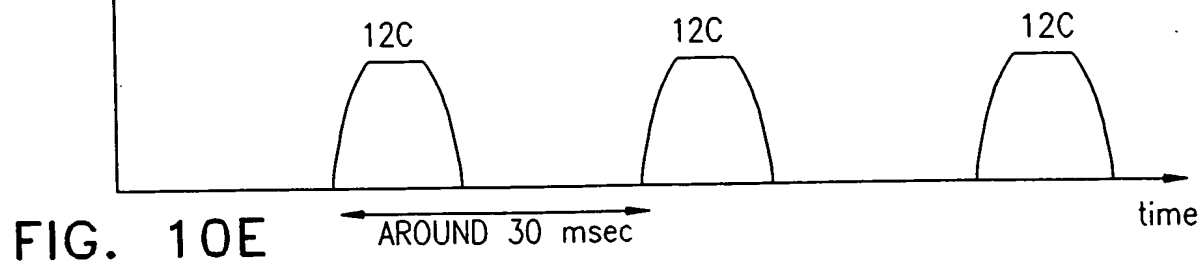
FIG. 10C



SIGNAL ON
SAMPLE DETECTOR



SIGNAL ON
SAMPLE DETECTOR



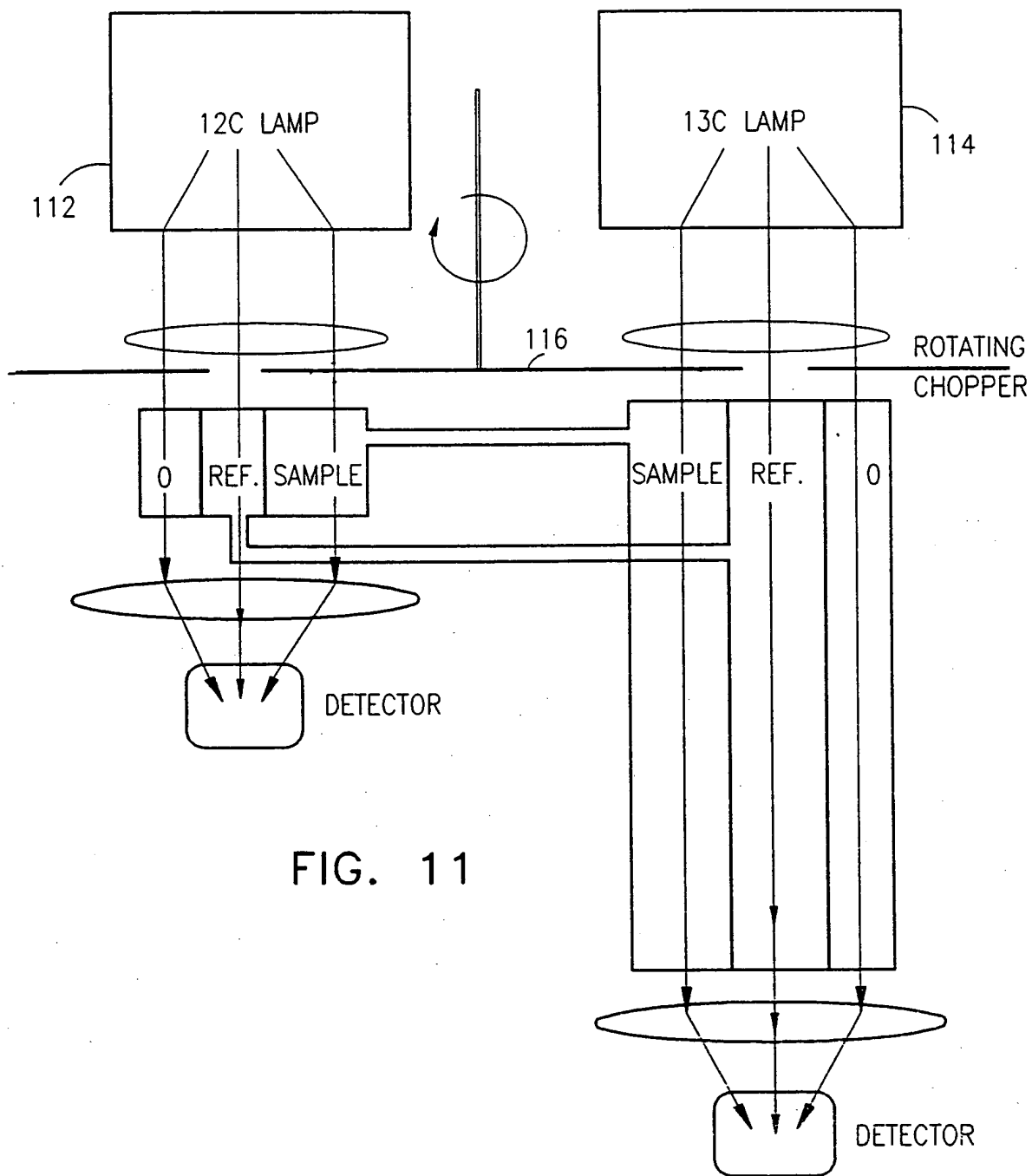


FIG. 11

FIG. 12

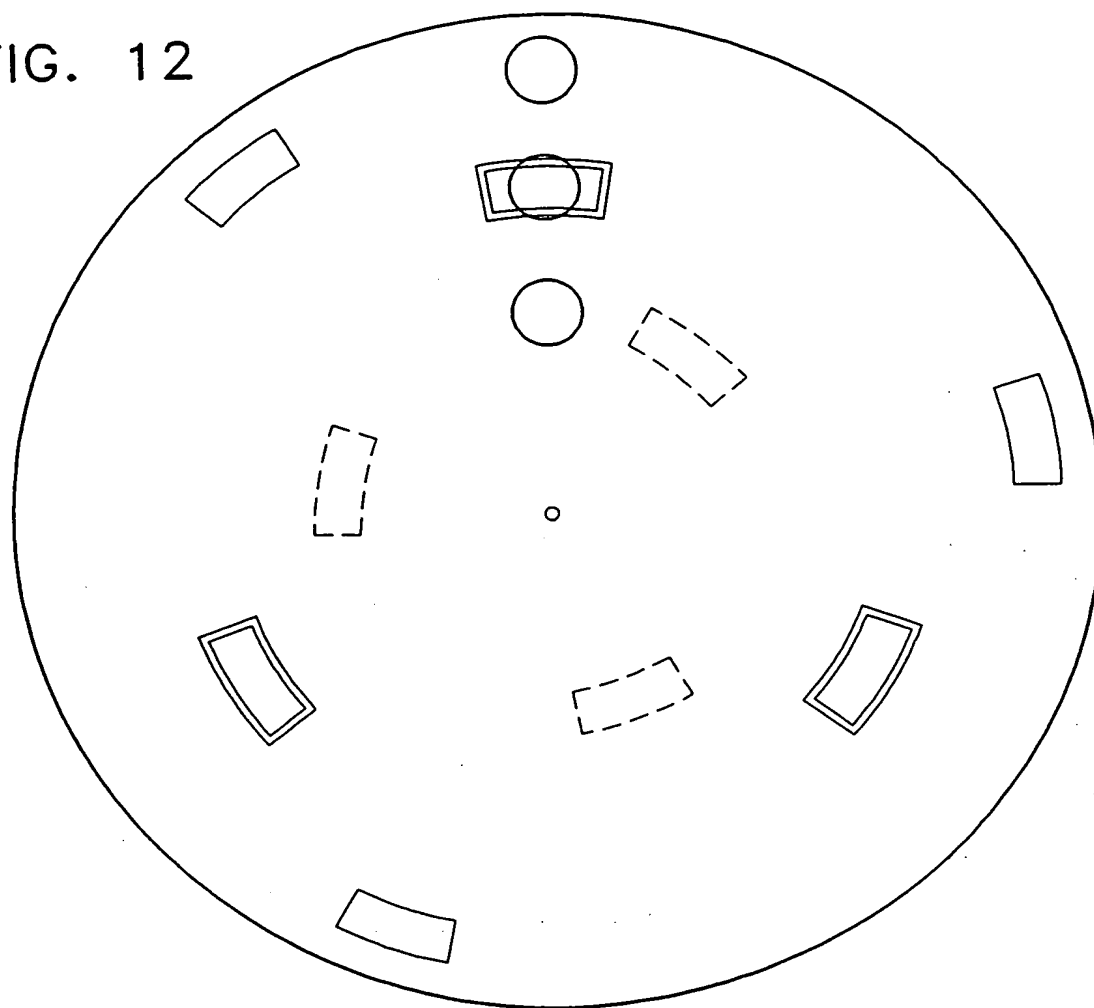


FIG. 13

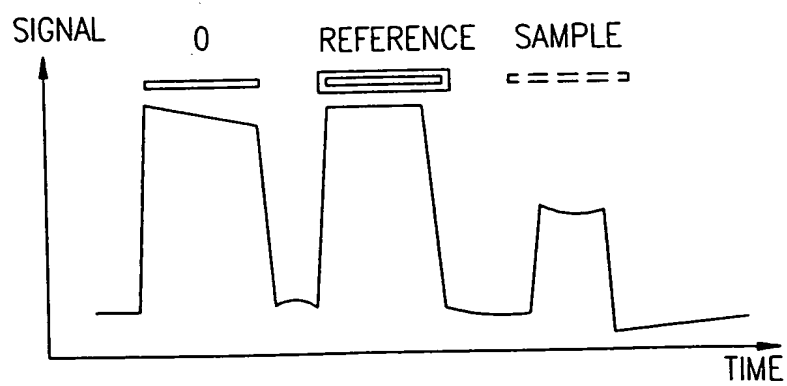


FIG. 14

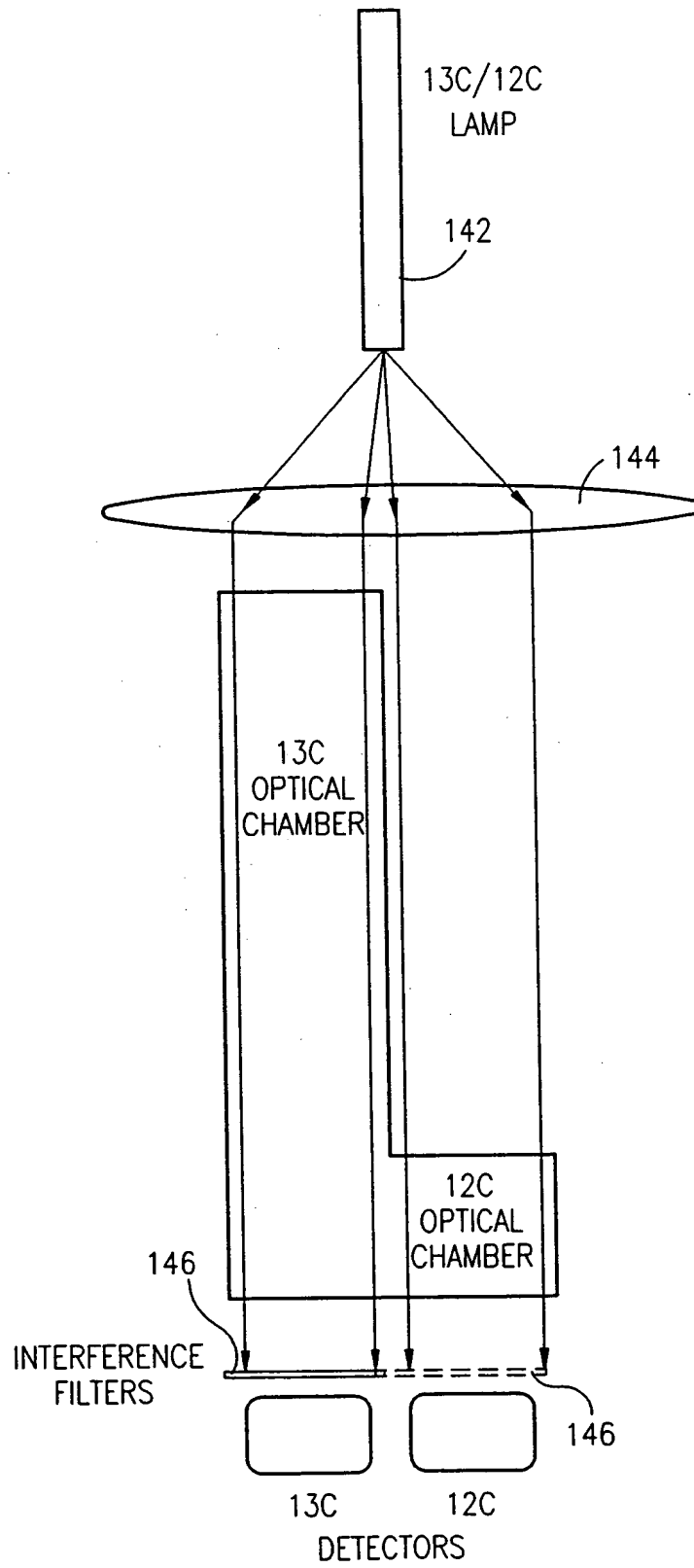


FIG. 15

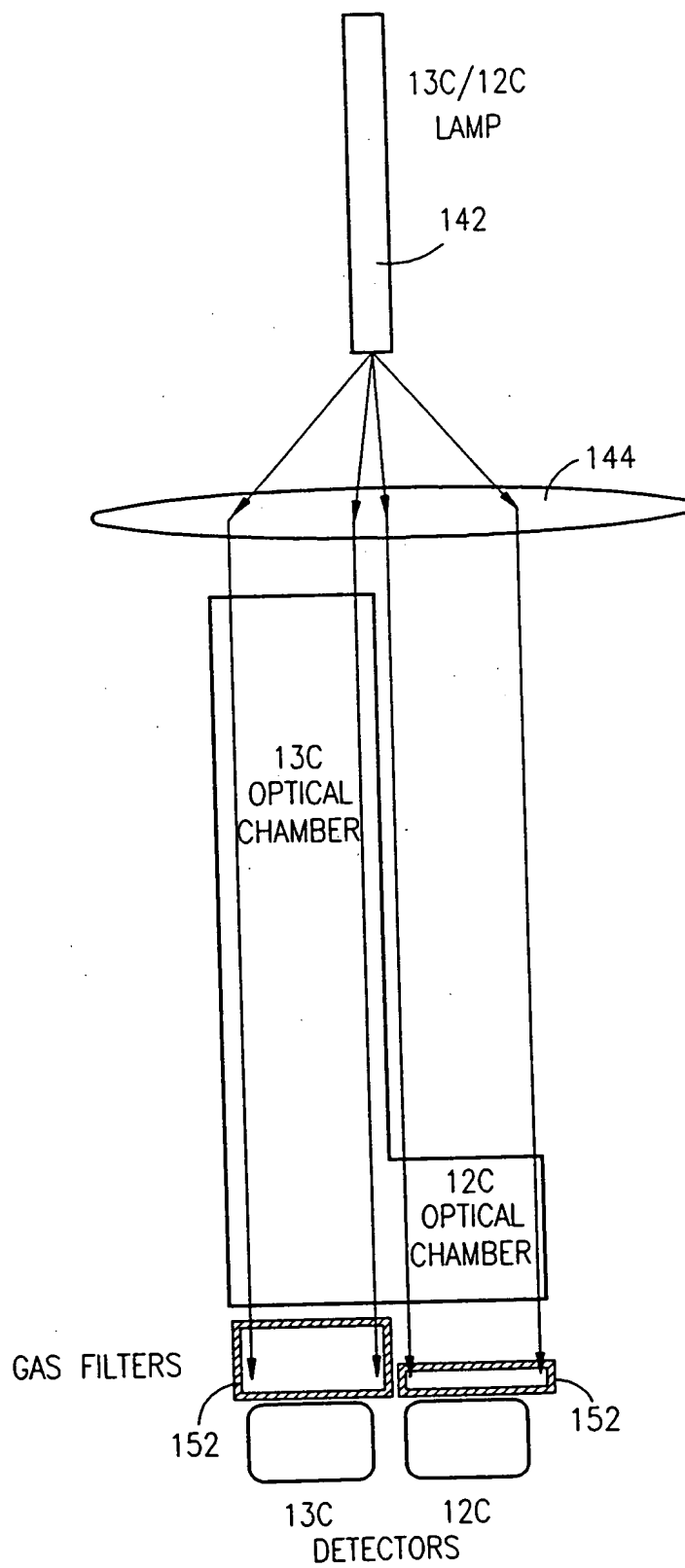


FIG. 16

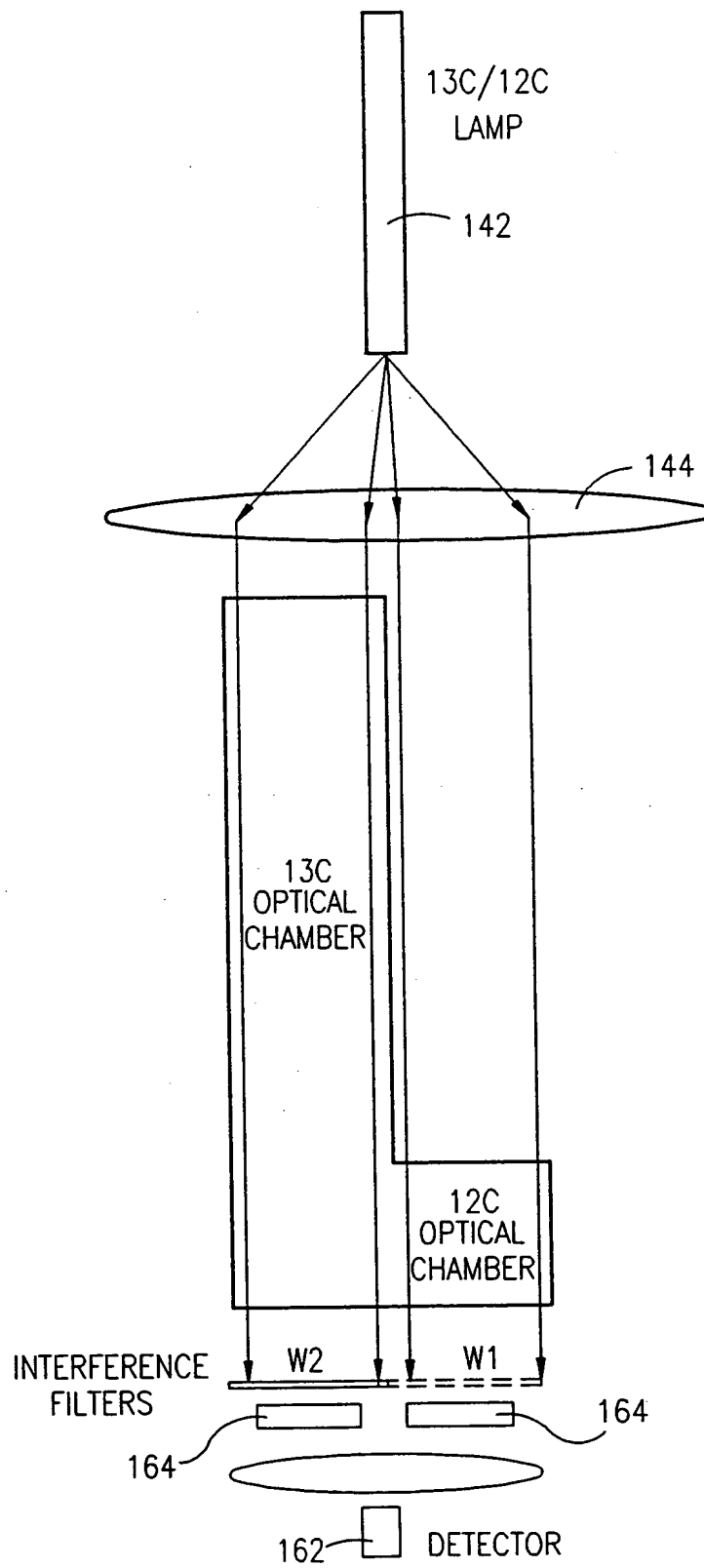


FIG. 17

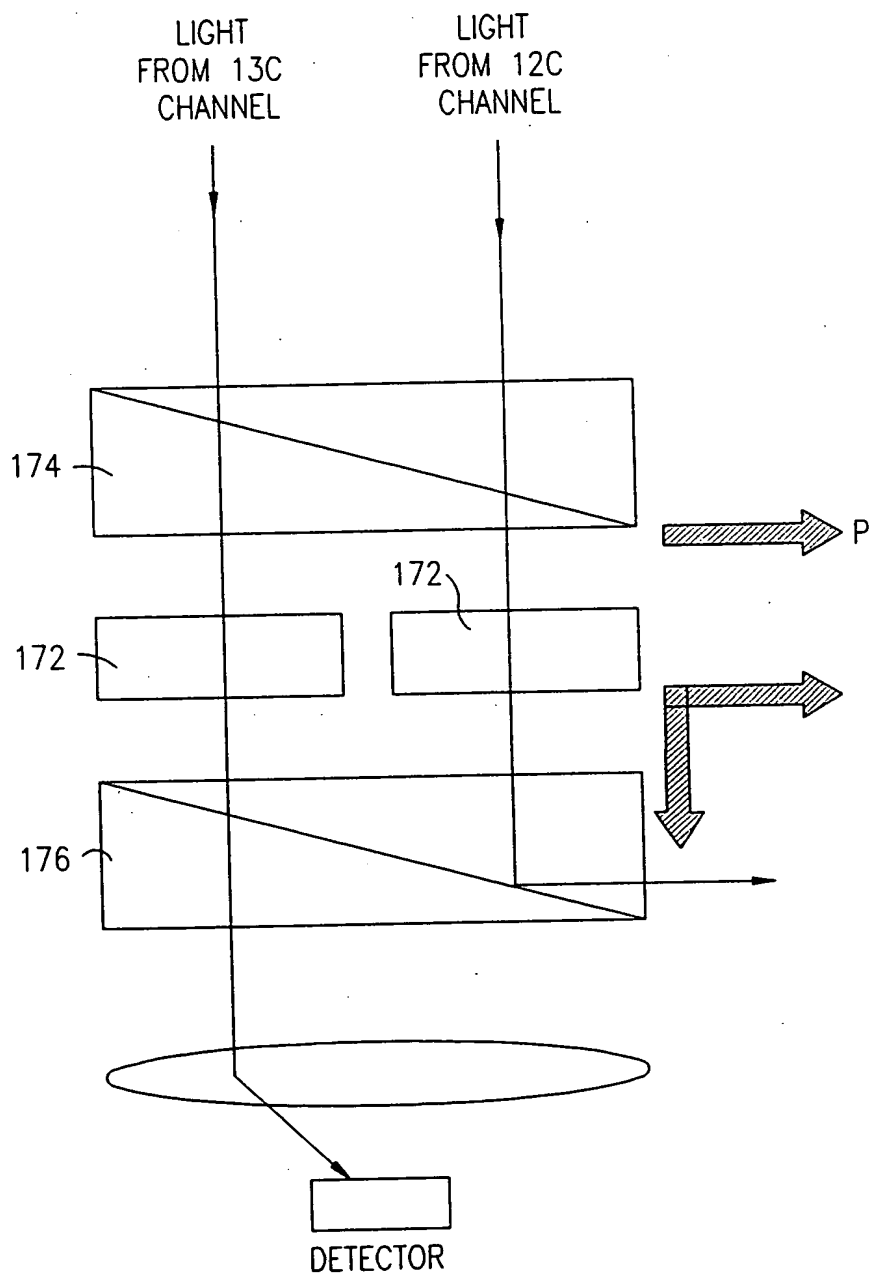


FIG. 18

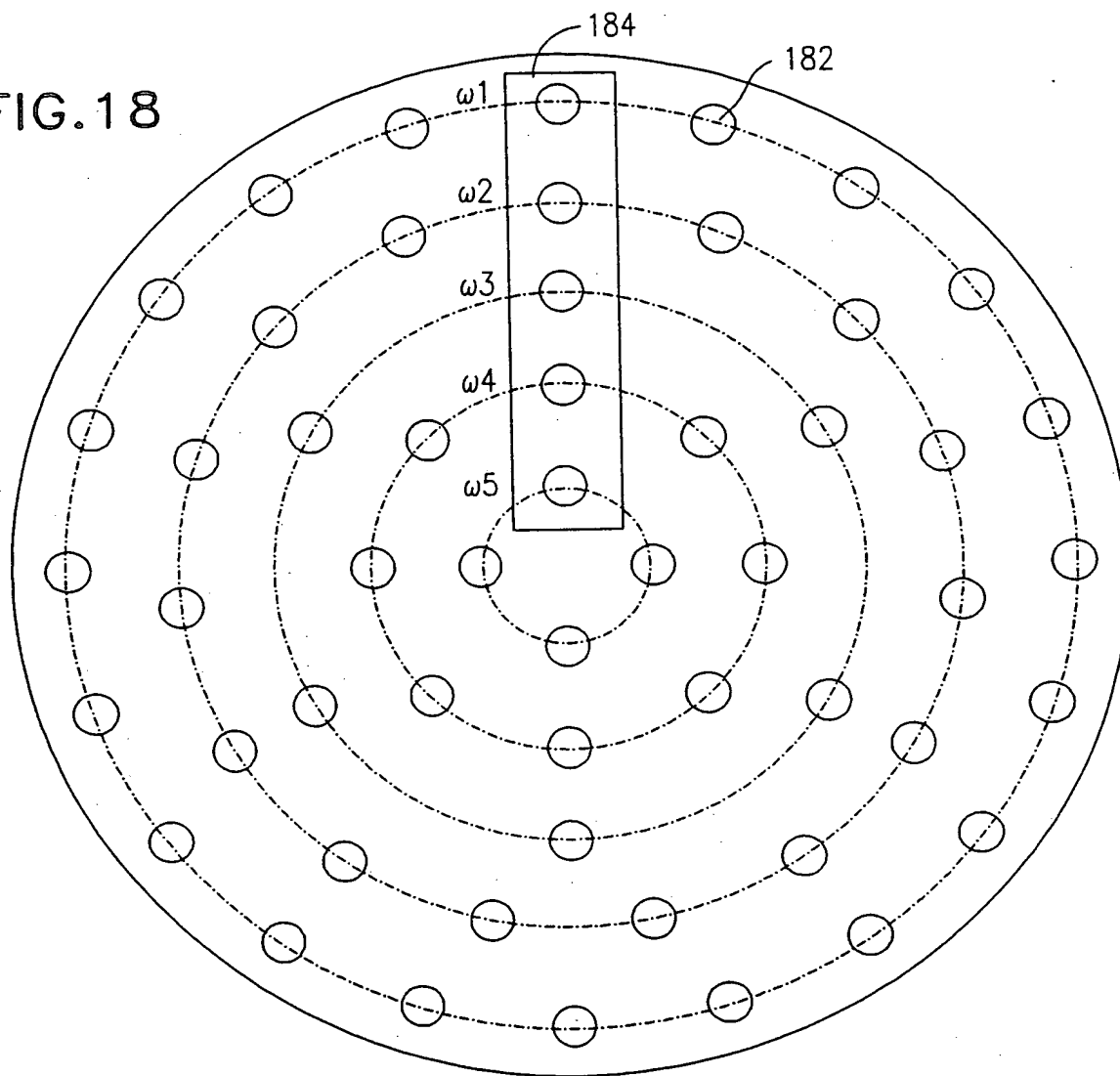


FIG. 19

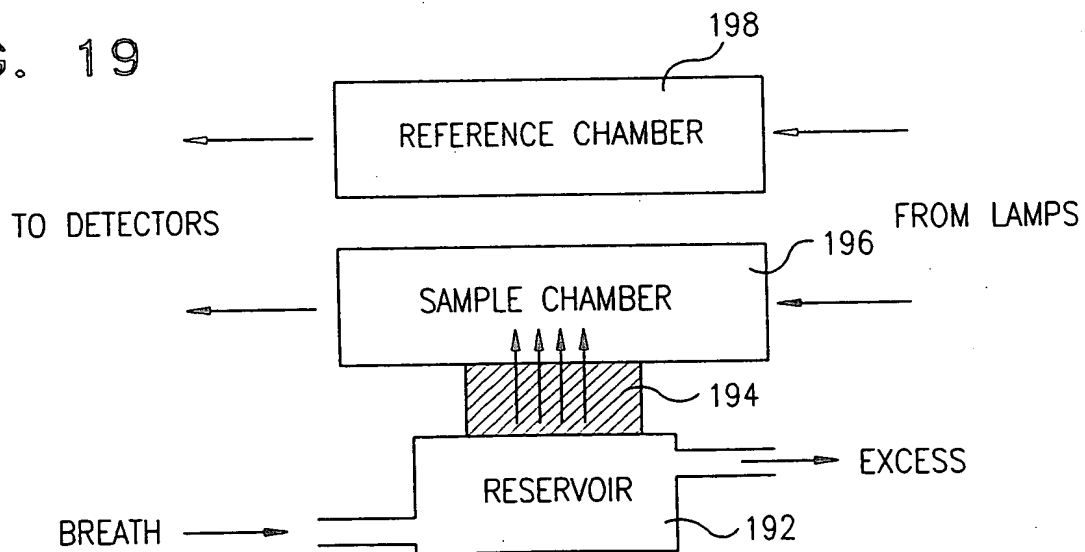


FIG. 20

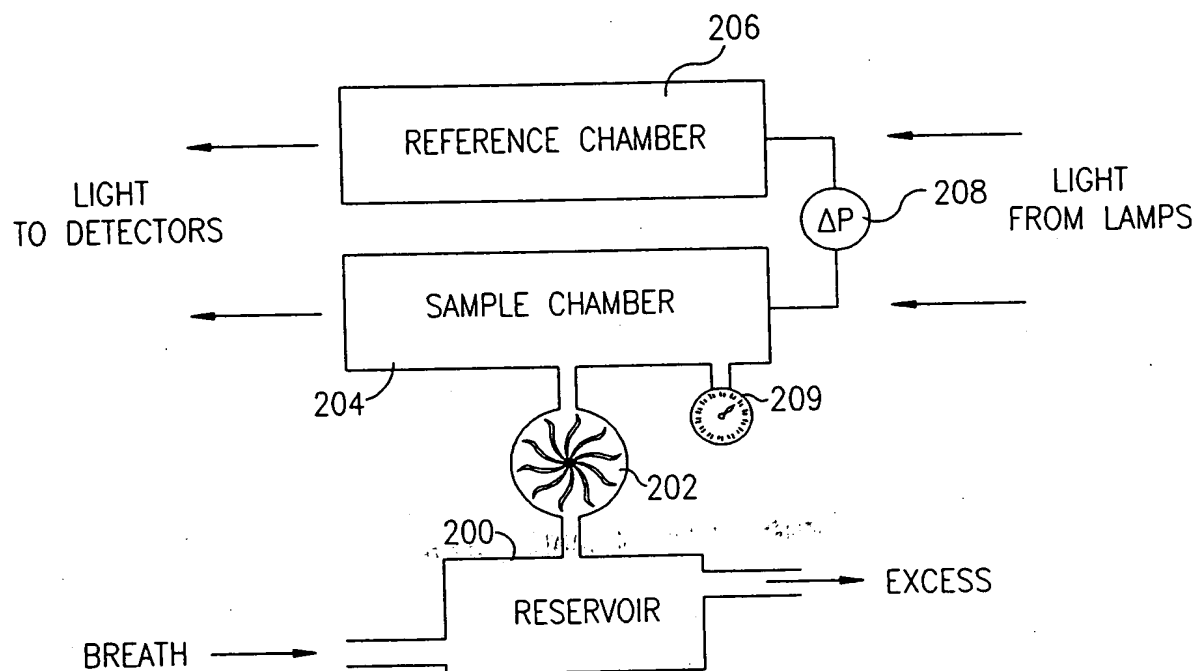
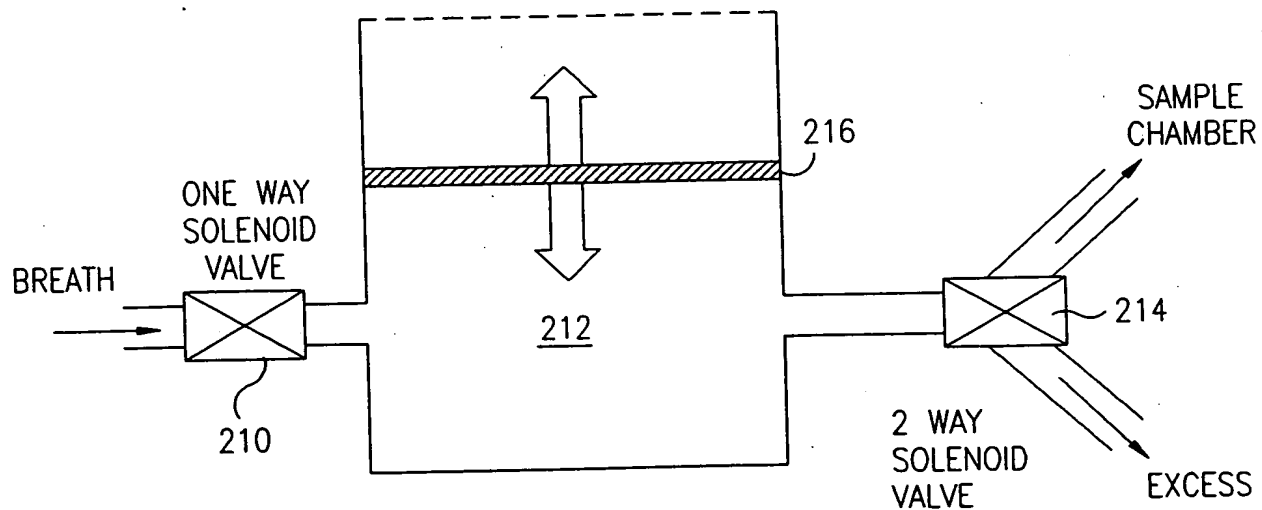


FIG. 21



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